SURGICAL ONCOLOGY CLINICS OF NORTH AMERICA

Surg Oncol Clin N Am
12 (2003) 105–126

# Hepatic artery embolization for hepatocellular carcinoma: technique, patient selection, and outcomes

Kamran Ahrar, MD*, Sanjay Gupta, MD

*Section of Vascular and Interventional Radiology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 325, Houston, TX 77030, USA*

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver [1]. The incidence of HCC is particularly high in southeast Asia and sub-Saharan Africa, but there is a clear rise in the number of cases in western Europe and the United States [2]. More than 90% of patients with HCC have underlying liver cirrhosis [3]. In patients with well-compensated cirrhosis, Child-Pugh class A or B disease (Table 1), partial hepatectomy should be considered [4]. Only a small proportion of patients with HCC are able to undergo surgical resection; in most patients with the disease, surgery is not a treatment option, either because of severe liver dysfunction caused by coexisting cirrhosis or because of the presence of multiple tumor nodules at diagnosis [4–6]. Following resection, overall 5-year survival rates range from 35% to 50% [4,6,7]. Even with curative resection, intrahepatic recurrence occurs in up to 70% of cases [8–11].

Orthotopic liver transplantation (OLT) has become widely accepted as therapy for HCC in cases in which anatomic or functional limitations preclude partial hepatectomy [4]. Best survival rates after OLT are achieved in patients with solitary HCCs of less than 5 cm in diameter or in patients with three or fewer tumor nodules, each less than 3 cm in diameter [12]. A limited number of patients qualify for OLT; furthermore, an even more limited number of donor organs are available for transplantation. This shortage of donor organs has resulted in an increase in the waiting time for OLT; as a result, 23% of the candidates originally placed on the waiting list for OLT become ineligible for the procedure because of disease progression [4].

* Corresponding author.
*E-mail address:* kahrar@mdanderson.org (K. Ahrar).


PII: S 1 0 5 5 - 3 2 0 7 ( 0 2 ) 0 0 0 8 9 - 3

Table 1
Pugh's modification of Child's grading of cirrhosis

| Measurement | 1 point | 2 points | 3 points |
|---|---|---|---|
| Bilirubin, mg/dL | 1.0–1.9 | 2.0–2.9 | >2.9 |
| PT prolongation (sec) | 1.0–4.0 | 4.0–6.0 | >6.0 |
| Albumin, g/dL | >3.5 | 2.8–3.4 | <2.8 |
| Encephalopathy[a] | None | 1 or 2 | 3 or 4 |
| Ascites | Absent | Slight | Moderate |

| Child-Pugh class | Total score | Hepatic function |
|---|---|---|
| A | 5 to 6 | Good |
| B | 7 to 9 | Intermediate |
| C | 10 to 12 | Poor |

[a] According to grading of Trey, Burns, and Saunders (1966).

*Abbreviation*: PT, prothrombin time.

*Data from* Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

In patients with HCC who require nonsurgical treatment, systemic chemotherapy and external-beam radiation therapy have failed to provide any significant survival benefit [13].

Over the past two decades, development of various interventional treatment options has revolutionized nonsurgical management of HCC. Modern interventional techniques for treatment of HCC may be categorized as local ablative or regional transcatheter therapies (Table 2). Of the local ablative therapies, percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are the most commonly used techniques. Various forms of catheter-directed therapy are currently in use, including transarterial embolization (TAE), transarterial chemoembolization (TACE) using solid particles (nonoily TACE), and TACE using ethiodized oil (Lipiodol, Laboratoire Guerbet, Aulnay-sous-Bois, France).

Table 2
Interventional treatment options for hepatocellular carcinoma

| |
|---|
| Local ablative therapies |
| Cryosurgery |
| Microwave ablation |
| Radiofrequency ablation[a] |
| Percutaneous ethanol injection[a] |
| Percutaneous acetic acid injection |
| Regional transcatheter therapies |
| Arterial chemoinfusion |
| Transarterial embolization[a] |
| Transarterial chemoembolization with solid particles[a] |
| Transarterial chemoembolization with ethiodized oil[a] |
| Transarterial radioembolization |
| $^{90}$Y microspheres |
| Lipiodol $^{131}$I |

[a] Commercially available and commonly used in the United States.

This article uses the term TACE to refer to transarterial chemoembolization using ethiodized oil unless otherwise specified.

PEI is effective in the treatment of small (<3 cm) nodular-type HCCs [14–16]. In prospective randomized trials, RFA has been shown to result in more reliable necrosis of small tumors and to require fewer treatment sessions than PEI for tumor ablation [17,18]. Local ablative therapies have a limited role in the treatment of large lesions or multifocal tumors.

The rationale for catheter-directed regional therapy for HCC rests on the observation that liver tumors derive almost all of their blood supply from the hepatic artery whereas normal liver tissue receives 80% of its blood supply from the portal vein [19,20]. Occlusion of the hepatic artery results in relatively selective ischemia within the tumor. Surgical ligation of the hepatic artery requires laparotomy and is only transiently effective because of rapid development of collateral vessels [21–23]. Catheterization and occlusion of the hepatic arteries and their branches feeding the tumor can be accomplished easily, however, and results in highly selective ischemia in the tumor bed.

## Technique

Since its introduction into clinical practice, transarterial therapy for HCC has evolved significantly. A better understanding of HCC in the setting of liver cirrhosis has resulted in significant modifications of hepatic artery embolization techniques.

Prior to any form of transarterial therapy, diagnostic visceral angiography is performed to determine the arterial anatomy, the blood supply to the tumor, and the patency of the portal vein, and to check for significant arterioportal shunting and signs of portal hypertension.

From the arterial anatomy and the extent of the tumor, a treatment plan is formulated. In reported studies, including randomized clinical trials conducted as recently as 1998, most investigators have treated the entire liver in one session after catheterization of the proper hepatic artery [24–26]. Today, modern imaging (digital subtraction angiography) and advanced catheter technology (3-French microcatheters) allow superselective catheterization of the arterial branches feeding the tumor. Selective (segmental or subsegmental) transarterial therapy is preferable to nonselective therapy, because a selective approach maximizes the impact of treatment on the tumor while decreasing collateral damage to tumor-free liver parenchyma [27–29]. When one whole lobe of the liver is involved, transarterial therapy is performed after catheterization of the right or left hepatic artery. In the case of bilobar disease, one lobe is treated at each session, allowing for recovery of tumor-free liver parenchyma prior to treatment of the contralateral lobe (Fig. 1).

TAE using gelatin sponge or polyvinyl alcohol (PVA) particles is the simplest form of catheter-directed therapy for HCC. Reduction of the blood flow provides favorable pharmacokinetics for intra-arterial chemotherapy

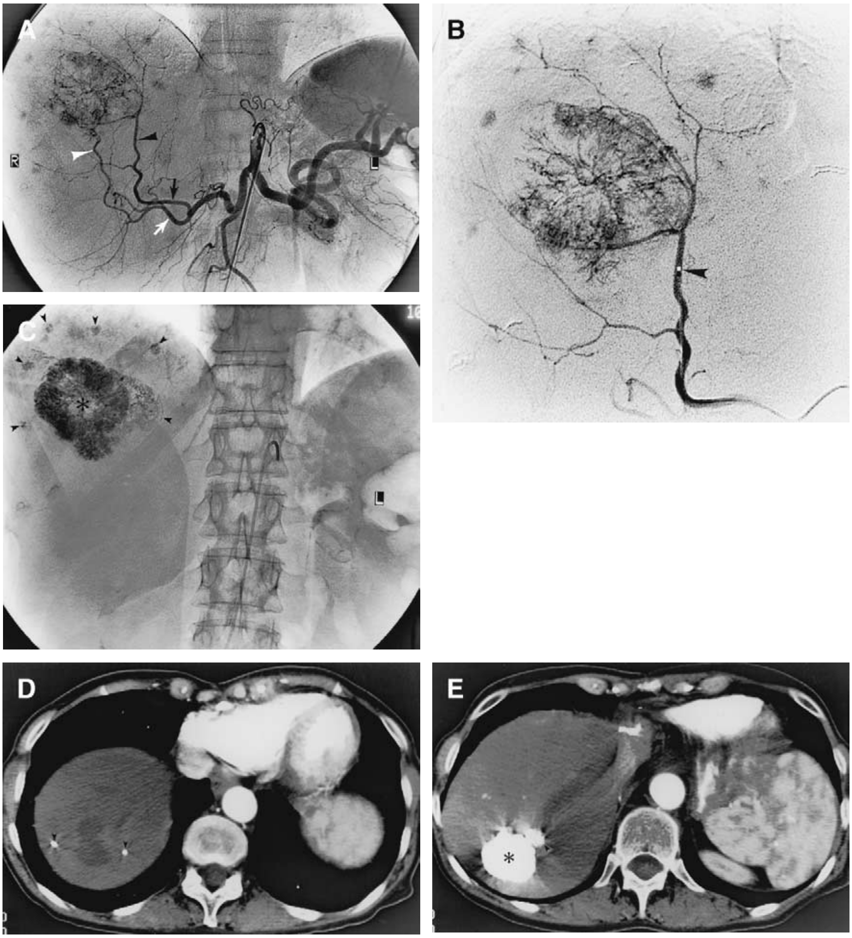


Fig. 1. A 61-year-old woman underwent two separate resections for hepatocellular carcinoma (HCC) in the left lobe of her liver. On follow-up, 21 months after the second resection, she was found to have recurrent HCC in the right lobe. She underwent intraoperative radiofrequency ablation (RFA) of three lesions in the right lobe. Four months after RFA, CT demonstrated a 3-cm lesion in the right lobe. The patient was referred for transarterial chemoembolization. (A) Selective celiac artery angiogram demonstrates a 3- to 4-cm hypervascular mass surrounded by at least five small hypervascular nodules not detected on CT, consistent with multifocal HCC. The largest nodule is supplied by two main arterial feeders: one (*black arrowhead*) arising from the posterior segmental branch (*black arrow*) of the right hepatic artery, and the second (*white arrowhead*) arising from the anterior segmental branch (*white arrow*) of the right hepatic artery. Oily chemoembolization was performed after selective catheterization of the two main feeders. (B) Superselective angiogram of the superior branch (*arrowhead*) of the posterior segmental branch of the right hepatic artery shows the main tumor as well as the satellite nodules. (C) Anteroposterior digital radiograph of the upper abdomen after chemoembolization demonstrates dense accumulation of Lipiodol in the main tumor (*asterisk*) and the satellite nodules (*arrowheads*). (D) Axial CT image of the abdomen in the early arterial phase demonstrates dense accumulation of Lipiodol in two small (<1 cm) nodules (*arrowheads*) in the dome of the liver. The area of low density between the two nodules is from previous RFA. (E) Axial CT image of the abdomen in the early arterial phase demonstrates dense accumulation of Lipiodol in the main tumor (*asterisk*) and a daughter nodule.

[30,31]; therefore, a chemotherapeutic agent is often added to the embolization regimen. Chemoembolization is a combination of targeted chemotherapy and arterial embolization that provides local chemotherapeutic and selective ischemic effects.

Chemoembolization has several theoretic advantages over other forms of regional transcatheter therapy [32]. First, embolization provides relatively selective ischemia within the tumor. Second, compared with simple intra-arterial chemoinfusion, chemoembolization provides much higher drug concentrations in the tumor [33,34]. Third, arresting arterial blood flow by injection of an embolic agent markedly prolongs the dwell time of the chemotherapy, with measurable drug levels present as long as a month after chemoembolization [35,36]. Finally, up to 85% of the chemotherapeutic drug is retained in the liver, minimizing systemic toxicity even at high doses [37].

In TACE, an emulsion of one or more chemotherapeutic agents in ethiodized oil is slowly injected into the selected artery under direct fluoroscopic guidance. Ethiodized oil is the ethyl ester of poppyseed oil and contains 38% iodine. Ethiodized oil has been used as a contrast agent for lymphangiographic studies. From the observation that ethiodized oil accumulates in liver tumors [38], Japanese investigators began incorporating the agent into transarterial chemotherapeutic regimens to improve tumor targeting [39].

Clinical and animal studies have demonstrated several advantages of chemoembolization with ethiodized oil over nonoily TACE. First, when ethiodized oil is injected intra-arterially, it is taken up in tumor tissue at a rate four times higher than the rate of uptake in normal liver [39]. Second, the viscous oil temporarily slows down the arterial circulation, decreasing washout of chemotherapy drugs. Third, ethiodized oil results in embolization not only of the arteries supplying the tumor but also of the venules supplying the tumor periphery. Although the hepatic artery is the major source of the blood supply to HCC nodules, the periphery of the tumor is nourished by small branches of the portal vein, which may persist and enlarge after embolization of the hepatic artery [20,40]. Ethiodized oil diffuses through the perisinusoidal arterioportal anastomoses and reaches the portal venules supplying the tumor, thus resulting in dual embolization and further devascularizing the tumor [41,42]. Finally, ethiodized oil may have vascular selectivity for large and mainly tumoral arteries [43,44]. Use of ethiodized oil results in significant improvement in the efficacy of treatment [35,45].

Ideal chemotherapeutic agents for TACE have not been identified as of this writing. Doxorubicin (Adriamycin) and cisplatinum (Platinol) are the two most commonly used agents. Cisplatinum may be associated with higher rates of tumor necrosis and patient survival [45,46]. Chemotherapy regimens commonly used in the United States include cisplatinum alone and cisplatinum in combination with doxorubicin and mitomycin C (Mutamycin) [32].

Following intra-arterial administration of the chemotherapeutic emulsion, the artery is embolized with absorbable gelatin sponge particles (Gelfoam particles). Embolization with Gelfoam particles enhances the necrotizing effect of the ethiodized oil-drug emulsion [47]. As opposed to steel coils, Gelfoam particles are degradable, and thus the patency of the feeding artery is maintained, permitting future TACE treatments.

When segmental, subsegmental, or unilobar TACE is employed, one or several sessions may be required to treat the entire tumor or tumors. Follow-up contrast-enhanced CT or dynamic contrast-enhanced MRI is performed 1 month after completion of therapy and at 3-month intervals thereafter [48].

Traditionally, hepatic artery embolization has been repeated at fixed intervals until an arbitrarily planned number of courses is reached, technical difficulties are encountered, or the patient dies [24–26]. Because repeated embolization may cause progressive liver atrophy, sequential procedures should be planned according to tumor response and patient tolerance [49,50].

## Side effects and complications

Most patients treated with hepatic artery embolization experience a combination of nausea, fever, and pain associated with leukocytosis and elevation of the liver enzymes. This so-called "postembolization syndrome" is treated symptomatically and may decrease in severity with subsequent chemoembolization sessions [51]. Chung et al [52] described predisposing factors for complications of TACE in 351 patients treated in 942 sessions. Fifteen percent of the patients had severe postembolization syndrome requiring treatment for 7 days or longer. Most of these patients had large tumors (>9 cm in diameter). The addition of Gelfoam particles increased the prevalence of severe postembolization syndrome among patients with tumors larger than 9 cm. Deterioration of liver function was observed in 15.4% of patients. In 9.7% of patients, liver function returned to pre-embolization status within 4 weeks, but in 5.7%, deterioration of liver function was permanent. Other complications were rare; they included hepatic infarction with coagulopathy (0.3%), intrahepatic biloma (0.8%), liver abscess (0.3%), tumor rupture with hemoperitoneum (0.8%), septicemia (2.6%), gastrointestinal bleeding (2.8%), and unintentional extrahepatic embolization, including gallbladder infarction (4.6%). Important predisposing factors for deterioration in liver function and for the other, less common complications were major portal vein obstruction, compromised hepatic functional reserve, biliary obstruction, previous biliary surgery, injection of an excessive amount (>20 mL) of ethiodized oil, hepatic arterial occlusion after repeated TACE, and nonselective embolization. Each of the patients with permanent deterioration in liver function had at least one of these predisposing factors. In addition to complications outlined previously, renal failure has been reported in 2.4%

of patients treated with chemoembolization for primary and metastatic liver tumors [53].

Chung et al [52] reported 9 deaths (2.6%) within 1 month after TACE. The overall mortality rate associated with TACE depends on the severity of the underlying liver disease and may reach 37% in patients with severe cirrhosis (Child-Pugh class C disease) [54]. With appropriate patient selection, the procedure-related mortality rate is less than 5% [35,55].

## Indications

Worldwide, patients with unresectable HCC are most commonly treated with TACE or other variations of hepatic artery embolization. In some parts of Asia, TACE is considered standard therapy for patients with unresectable HCC [7,56]. For patients with acute tumor rupture, pain, or a paraneoplastic syndrome, such as hypoglycemia or hypercalcemia, hepatic artery embolization is effective and may be life-saving [57,58]. In patients awaiting OLT, chemoembolization may help control the growth of the tumor and prevent progression of HCC. The benefits of pretransplant chemoembolization reported in individual series have not been studied in prospective randomized controlled trials; nevertheless, many transplant centers use TACE to prevent drop-out of candidates from the waiting list [12,59–61]. TACE has been evaluated as both neoadjuvant and adjuvant therapy in patients who qualify for partial hepatectomy. Conflicting results have been reported [46,62–64].

## Contraindications

Patients with severe anaphylactoid reactions to radiographic contrast media, uncorrectable coagulopathy, severe renal insufficiency, or severe peripheral vascular disease precluding catheterization of tumoral arteries cannot be treated with hepatic artery embolization.

Hepatic encephalopathy and jaundice are absolute contraindications to hepatic artery embolization. Biliary obstruction and dilated bile ducts, even with a normal bilirubin level, increase the risk of liver infarction [65]. The main reason that arterial embolization is well tolerated is the dual blood supply to the liver. Therefore, portal venous blood flow must be carefully assessed prior to arterial embolization. Chemoembolization can be performed safely in patients with main portal vein occlusion as long as hepatopetal collateral flow is present [66]. With increasing parenchymal disease, the liver depends more heavily on the hepatic artery rather than the portal vein. In a subgroup of patients with parenchymal liver disease, arterial embolization is associated with increasing risk of liver failure. The constellation of findings in this group of patients includes involvement of greater than 50% of the liver by tumor, a lactate dehydrogenase level greater than 425 IU/L, an aspartate aminotransferase level greater than 100 IU/L, and a total serum bilirubin level of 2 mg/dL or greater [67].

## Patient selection

There are no standard guidelines for selecting appropriate patients for TACE; however, characterization of prognostic factors may help in choosing appropriate candidates for this therapy. The size of the tumor is the most important prognostic factor in patients treated with TACE [68–71]. An impressive 67% 4-year survival rate has been reported in patients with HCCs smaller than 4 cm treated with subsegmental TACE [29]. Ikeda et al [68] demonstrated that patient survival is directly related to the best tumor response to transarterial treatment. Tumor necrosis is directly related to the extent of ethiodized oil accumulation in the tumor [27,28,71,72]. As significant tumor necrosis is rarely achieved in larger tumors [73], it is not surprising that TACE is less effective in improving the survival of patients with larger HCCs [74].

Important factors adversely affecting survival in patients treated with TACE include severe underlying cirrhosis, the presence of ascites, an elevated bilirubin level, and the presence of extrahepatic metastases [70]. Bronowicki et al [75] demonstrated significantly improved survival in patients with limited liver dysfunction, Okuda stage I or II (Table 3) or Child class A or B disease but not in those with decompensated liver disease (Okuda stage III or Child class C disease). The extent of the tumor in unilobar or bilobar disease was a significant prognostic factor in one study [70]. In another study, severe liver dysfunction, the presence of intrahepatic metastases, and increased frequency of transarterial treatment were slightly correlated with reduced survival after hepatic artery embolization, but did not reach statistical significance [69]. Clinical features that adversely affect survival and are commonly accepted as exclusion criteria are listed in Table 4.

Table 3
Okuda prognostic grading

| Factor | Score |
|---|---|
| Tumor >50% of liver | 1 |
| Ascites present | 1 |
| Serum albumin <3 g/dL | 1 |
| Serum bilirubin >3 mg/dL | 1 |
| **Total score** | **Stage** |
| 0 | I |
| 1 or 2 | II |
| 3 or 4 | III |

*Adapted from* Okuda K, Ohtsuki T, Obatta H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Cancer 1985;56:918–28.

Table 4
Suggested contraindications of TACE for hepatocellular carcinoma*

| |
|---|
| Portal vein occlusion |
| Main trunk or its first-order branches |
| Extrahepatic metastases |
| Advanced age |
| >80 y (Pelletier et al, 1998) |
| >70 y (Madden et al, 1993) |
| Severe hepatic disease[a] |
| Encephalopathy |
| Bilirubin >3.0 mg/dL |
| Albumin <3.0 g/dL |
| Clinical ascites requiring treatment |
| Prothrombin activity <30% of normal |
| Okuda stage III |
| Variceal bleeding |
| Surgical portocaval anastomosis |

*Abbreviation*: TACE, transarterial chemoembolization.

[a] Although not directly cited, Child-Pugh class C disease is implied as an exclusion criterion.

* Compiled from exclusion criteria reported in randomized controlled trials (24–26,82,84).

## Results

Worldwide, there is significant experience with catheter-directed treatment of liver tumors. Because of large differences between studies in patient demographics, underlying types and stages of liver disease, chemotherapy agents and doses employed, embolization agents employed, vascular techniques, frequency of therapy, and intervals between treatment sessions, it is difficult, if not impossible, to make a general statement about the efficacy of catheter-directed therapy for HCC. Nevertheless, the studies performed to date provide some useful data.

Complete tumor necrosis has been reported in 37% to 54% of cases after one session of TACE [76,77]. In a prospective randomized controlled trial, TAE significantly improved patient survival when compared with systemic chemotherapy [77]. With the pharmacokinetic advantages of chemoembolization and tumor-targeted therapy with ethiodized oil, TAE has fallen out of favor in recent years. Nevertheless, 1- and 2-year survival rates of 50% and 33% have been reported with particle embolization [79]. Transarterial infusion of an emulsion of a chemotherapeutic agent in ethiodized oil followed by arterial embolization with Gelfoam particles (TACE) is more effective than nonoily chemoembolization, transarterial infusion of ethiodized oil alone, or transarterial infusion of ethiodized oil with a chemotherapeutic agent [35,47]. With the TACE regimen, 1-, 2-, 3-, and 4-year survival rates of up to 64%, 38%, 27%, and 27%, respectively, have been achieved [74,75,80]. The best results reported to date are from a study in which Matsui et al [29] treated 100 patients with small HCCs (<4 cm in diameter) with subsegmental TACE. The 1-, 2-, 3-, and 4-year survival rates in 82 patients were 100%, 92%, 78%, and 67%, respectively. Of the tumors resected surgically after subsegmental TACE, 7 of 11 (64%) demonstrated complete necrosis.

Initial randomized trials (Table 5) failed to show a statistically significant survival benefit in patients treated with transarterial therapy. This apparent lack of benefit may be from the use of outdated techniques. The techniques used in these trials were probably obsolete prior to the completion of each study. The results of these trials are at best inconclusive, if not misleading. Simonetti et al [81] attempted a systematic review of randomized controlled trials of treatment of HCC. For a group of patients treated with transarterial embolization, the authors identified five randomized controlled trials involving patients with both compensated and decompensated liver disease who were treated with remarkably different protocols [24,25,78,82,83]. Given the inhomogeneous character of this group, the authors suggested using caution in reviewing the results; nevertheless, they reported slightly better survival in the treated patients [81].

More recently, a detailed analysis of six randomized controlled trials (Table 5) that compared arterial embolization with conservative management [24–26,78,82,84], including four of the five trials reviewed by Simonetti et al [81], highlighted several shortcomings with each of the studies (Table 6) [85]. Three of these trials [24–26] are frequently cited by various authors and deserve closer attention.

In 1990, Pelletier et al [24] reported the results of a randomized controlled trial in which 42 patients with inoperable HCC were randomly assigned to TACE or palliative treatment. There was no difference in survival between the two groups. Patients in the treatment group underwent TACE with doxorubicin and Gelfoam powder injected simultaneously in the proper hepatic artery. This study has been criticized for its suboptimal methodology. First, the authors did not use ethiodized oil as a conjugate with the doxorubicin. Instead, they injected Gelfoam powder, an embolization agent that is more harmful to nontumerous liver than larger Gelfoam particles [86,87]. Second, the authors performed chemoembolization in a nonselective fashion, exposing tumor-free liver parenchyma to cytotoxic agents and ischemia while undermining effective targeted delivery to the tumor. Finally, the authors repeated the treatment at planned periodic intervals (at 2, 6, and 12 months after the initial treatment) rather than on the basis of patient tolerance and tumor response.

The second frequently cited multicenter randomized controlled trial of TACE versus palliative treatment failed to demonstrate a statistically significant survival advantage in the treated patients; however, it showed a trend toward improved survival in the treatment group [25]. The 1-year survival rate among the treated patients was 62%, compared with 43.5% in the untreated group. Furthermore, in patients treated with TACE, tumor growth was reduced and the incidence of portal obstruction was lower. This

Table 5
Essential features of randomized controlled trials of TACE and TAE in patients with hepatocellular carcinoma*

| | | | | | Survival (TACE or TAE vs. Control) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Courses[a] | Drugs | Control treatment | 1-year | 2-year | 4-year | $p$ |
| Lin et al, 1998 [78] | 63 | 2.1 | PVA or G (powder) | 5-FU | 42% vs. 13% | 25% vs. 13% | NR | 0.01 |
| Pelletier et al, 1990 [24] | 42 | 2 | D, G (powder) | Palliative | 24% vs. 31% | NR | NR | NS |
| Madden et al, 1993 [82] | 50 | 0.8 | E, L | Palliative | Median: 48 vs. 51 days | | | NS |
| Cooperative French Group 1995 [25] | 96 | ‡ | C, L, G (particles) | Palliative | 62% vs. 43.5% | 38% vs. 26% | 13% vs. 10% | NS |
| Bruix et al, 1998 [84] | 80 | 2.2 | G (particles), coils | Palliative | NR | 49% vs. 50% | 13% vs. 27% | NS |
| Pelletier et al, 1998 [26] | 73 | 3[fl] | C, L, Le, G (particles), T | T | 51% vs. 55% | 24% vs. 26% | NR | NS |

*Abbreviations*: C, cisplatinum; D, doxorubicin; E, epirubicin; 5-FU, 5-fluorouracil; G, gelfoam; Le, lecitin; L, lipiodol; n, number of patients; NR, not reported; NS, not significant; PVA, polyvinyl alcohol particles; TACE, transarterial chemoembolization; TAE, transarterial embolization; T, tamoxifen.

* *Adapted from* Trevisani F, De Notariis S, Rossi C, et al. Randomized control trials. Is there room for new studies? J Clin Gastroenterol 2001;32:383–9.

[a] Mean number of courses of TACE or TAE.

‡ Every 2 mo × 4 courses (achieved in 52%).

fl Median (TACE every 3 mo × 4 courses, then every 4 mo).

Table 6
Characteristics of randomized controlled trials on TACE in patients with HCC

| Variable | Pelletier et al, 1990 [24] | Madden et al, 1993 [82] | Cooperative French Group, 1995 [25] | Bruix et al, 1998 [84] | Pelletier et al, 1998 [26] |
|---|---|---|---|---|---|
| Patient selection | Appropriate | Poor[a] | Appropriate | Appropriate | Appropriate |
| TACE technique | Suboptimal | Suboptimal | Suboptimal | Suboptimal | Suboptimal |
| Use of lipiodol | No | Yes | Yes | No | Yes |
| Optimized lipiodol drug emulsion | NA | NR | NR | NA | No[b] |
| Selective catheterization of arterial feeders | No | No | No | Yes | No |
| Gelfoam particles following lipiodol drug emulsion | No | No | Yes | No | Yes |
| Treatment plan | Suboptimal | Suboptimal | Suboptimal | Adequate | Suboptimal |
| Tailored to patient tolerance and tumor response | No | No | No | Yes | No |
| Deviation from protocol | Acceptable | Significant | Acceptable | None | Acceptable |
| Patients in the treatment group left untreated | 4.80% | 28.00% | 4.20% | None | 5.40% |

*Abbreviations*: HCC, hepatocellular carcinoma; NA, not applicable; NR, not reported; TACE, transarterial chemoembolization.

[a] Most patients (86%) had advanced disease, Okuda stage II or III, 22% of treated group with Okuda III disease.

[b] Small-droplet oil-in-water emulsion.

benefit was offset by the high incidence of liver failure (60%), which may be partially explained by the suboptimal therapeutic approach adopted in this study. TACE was performed in a nonselective fashion with chemoembolization of the proper hepatic artery rather than specific arterial branches feeding the tumor and was repeated at fixed, planned intervals (every 2 months for a maximum of four courses). It is conceivable that this aggressive treatment regimen caused repeated iatrogenic insult to the liver, exacerbating the underlying liver disease. The statistical analysis of this study deserves exploration. A triangular test was used to set up stopping boundaries for the trial. The survival rate with palliative treatment was assumed to be 50%. It was further assumed that TACE would have to yield a survival rate of 75% to be superior to palliative treatment. An interim analysis of the results after enrollment of 96 patients demonstrated an increase of less than 50% in the survival rate with TACE as compared with palliative treatment. Therefore, the trial was stopped, despite a 20% survival advantage in the treated patients at 1 year. It appears that a larger sample size would be necessary to evaluate the significance of this finding.

In the third frequently cited randomized controlled trial, 73 patients were randomly assigned to receive tamoxifen alone or tamoxifen plus TACE [26]. Chemoembolization was performed in a nonselective manner at fixed intervals (every 3 months during the first year and every 4 months thereafter). The rate of objective tumoral response (at least 50% reduction in tumor bulk) was 24%. TACE did not improve patient survival compared with survival after tamoxifen alone, however. The benefit of inhibiting tumor growth was probably offset by worsening liver function in patients with cirrhosis whose entire liver was treated repeatedly with TACE. More important, the authors used oil-in-water emulsion (small droplets of ethiodized oil dispersed in aqueous solution of cisplatinum), which of all the possible ethiodized oil drug emulsions is the one with the lowest embolic effect and which does not improve either ethiodized oil or drug targeting of tumor vessels [43,44]. The authors pointed out that this critical information about the drawbacks of oil-in-water emulsions did not become available until after initiation of the trial [26].

Another randomized controlled trial, published in 1994, demonstrated no difference in survival rates between patients treated with TACE (cisplatinum, ethiodized oil, and Gelfoam particles) and those treated with TAE (ethiodized oil and Gelfoam particles) [88]. For the patients treated with TACE, the authors reported mixing as little as 5 mL of ethiodized oil with 20 mL of aqueous cisplatinum solution (14.5 mL of ionic contrast medium and 5 mL of normal saline), probably resulting in a small-droplet oil-in-water emulsion. More recently, this type of emulsion has been shown to generate a low embolic effect, a high lung uptake, and a low ratio of tumor to nontumerous liver uptake [43]. Large-droplet water-in-oil emulsions are recommended for best results.

Given the suboptimal techniques employed in these randomized controlled trials, the role of hepatic artery embolization in treatment of patients with unresectable HCC remained controversial for many years.

More recently, two excellent randomized clinical trials have shown significant survival advantage in patients treated with TACE when compared with those treated symptomatically [89,90].

In one study, Chinese investigators randomized 80 Asian patients with newly diagnosed unresectable HCC to TACE or symptomatic treatment [89]. Chemoembolization was performed using an emulsion of cisplatin in Lipiodol and gelatin-sponge particles and was repeated every 2 to 3 months unless there was evidence of contraindications or progressive disease. TACE resulted in marked tumor response and significantly better survival (1 year, 57%; 2 years, 31%; 3 years, 26%) when compared to the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; $P = 0.006$).

In a similar trial, Spanish investigators randomized 112 European patients to TACE, bland embolization, or symptomatic treatment [90]. Patients in TACE group received an intraarterial emulsion of doxorubicin in Lipiodol, followed by Gelfoam fragments to achieve flow stagnation. Survival probabilities at 1 year and 2 years were 82% and 63% for TACE, 75% and 50% for bland embolization, and 63% and 27% for symptomatic treatment group (TACE vs. symptomatic treatment $P = 0.009$).

High rates of recurrence after curative resection of HCC have provided the impetus for evaluation of TACE as both neoadjuvant and adjuvant therapy. In a randomized trial of TACE as neoadjuvant therapy prior to resection of large tumors (>10 cm), those treated with TACE had a significantly worse overall survival during a 10-year period [62]. In those treated with TACE, surgery was delayed for 4 months and a higher incidence of distant metastases was reported. Reduction of tumor size by TACE, however, may render inoperable patients resectable. Majno et al [46] reported downstaging 21 of 49 patients (42%), allowing resection in 10% of previously unresectable cases.

To study the effect of adjuvant therapy after curative hepatic resection in patients with HCC, Izumi et al [63] randomly assigned 50 patients to TACE or no treatment. Disease-free survival was significantly improved in those patients who underwent one course of TACE. The 1-, 2-, 3-, and 4-year disease-free survival rates were 64.5%, 54.9%, 32%, and 25.6%, respectively, for the treatment group, versus 43%, 22%, 11.7%, and 5.9%, respectively, for the control group. The recurrence rate in the treated group was lower than the control group, but the difference did not reach statistical significance. The cumulative survival or survival after a recurrence between patients with or without adjuvant therapy was not significantly different. Lai et al [64] randomly assigned 66 patients to a combination of intravenous chemotherapy and TACE or no treatment after partial hepatectomy. Patients who received adjuvant chemotherapy had a higher incidence of extrahepatic metastases and significantly worse survival outcome. The respective disease-free survival rates at 1, 2, and 3 years were 50%, 36%, and 18% for the treatment group and 69%, 53%, and 48% for the control group. Optimal TACE techniques were not used in either one of the studies.

Randomized controlled trials have helped clarify the natural history of HCC in patients with compensated cirrhosis. The large discrepancy between the survival benefits reported in nonrandomized studies and those reported in randomized controlled trials is mostly from an underestimation of survival in historic cohorts used as control groups in some nonrandomized trials. Traditionally, the prognosis of patients with untreated HCC was believed to be extremely poor, with a median survival time of 1.6 months reported for patients in the Far East [91]. For unselected patients in the West, a median survival time of 14 weeks and a 1-year survival rate of 13% have been reported [92]. A recent analysis of 102 cirrhotic patients with HCC, who qualified for TACE but were randomly assigned to the palliative treatment arm within prospective randomized controlled trials, demonstrated overall 1-, 2- and 3-year survival rates of 54%, 40%, and 28%, respectively [93]. Four independent predictors of mortality were identified, including poor performance status, constitutional syndrome, vascular invasion, and extrahepatic spread. In the absence of adverse factors, the 1-, 2-, and 3-year survival rates were 80%, 65%, and 50%, respectively, versus 29%, 16%, and 8% for patients with at least one adverse factor. It is clear that these adverse factors and survival rates should be taken into account in the design and analysis of clinical trials. Furthermore, a large number of patients may be necessary to demonstrate a presumably small but significant survival benefit.

## Combination of TACE and other interventional treatments

PEI and RFA are not as effective in the treatment of larger HCCs (>3 cm) as they are in the treatment of smaller tumors [17,94]. Larger tumors may be treated with TACE; however, complete necrosis may not be achieved despite repeated treatment sessions. A combination of interventional procedures may overcome limitations of individual treatment options.

The combination of TACE and PEI as a therapeutic option has been reported to be superior to each individual treatment alone [95–101]. Tanaka et al [95] reported 1-, 2-, and 3-year survival rates of 100%, 85%, and 85%, respectively, for patients with solitary HCCs larger than 3 cm. The rationale for this combination hinges on three assumptions: first, TACE causes necrosis of the tumor and disruption of intratumoral septa, which in turn facilitate homogeneous distribution of ethanol during PEI therapy; second, chemoembolization results in formation of a fibrous capsule, limiting diffusion of alcohol beyond the tumor; third, after arterial embolization, the washout rate of ethanol from the tumor is significantly diminished, resulting in a longer dwell time and more effective ablation. Lencioni et al [98] reported 3- and 5-year survival rates of 69% and 47% in a group of patients with compensated cirrhosis and large tumors (3–9 cm) occurring as a single nodule or in association with no more than two nodules. Patients with Child-Pugh class A cirrhosis had better 3- and 5-year survival rates (75% and 59%, respectively). In a randomized controlled trial, Koda et al [101] demonstrated a significantly decreased rate of recurrent HCC in patients treated with a combination of TACE and PEI compared with the recurrence rate in patients treated with PEI alone.

Hepatic artery embolization or balloon occlusion may be combined with RFA to generate a larger area of ablation. The rationale for this combination is based on the fact that perfusion-mediated tissue cooling limits the area of thermal necrosis [102]. With temporary disruption of portal vein and hepatic arterial flow, larger areas of thermal necrosis can be created during RFA [102,103]. Rossi et al [104] reported their preliminary experience with this technique in 62 patients with large HCCs (3.5–8.5 cm). Forty patients underwent RFA during balloon occlusion of the hepatic artery, and the remaining 22 patients underwent segmental arterial embolization prior to RFA. Follow-up spiral CT demonstrated complete necrosis in 56 patients after a single treatment session with RFA. The remaining 6 patients underwent repeat RFA with balloon catheter occlusion of the hepatic artery. Follow-up CT demonstrated complete necrosis in all 6 patients.

## Summary

Most patients with HCC do not qualify for surgical interventions. In carefully selected patients, TACE may improve survival, reduce the rate of tumor growth, and decrease the incidence of portal vein occlusion. Since the introduction of TACE in the 1980s, the technical aspects of the procedure have significantly improved. Sophisticated angiographic equipment and techniques have made superselective arterial catheterization possible for more focused drug delivery. The use of ethiodized oil allows for more effective targeting of HCC and provides dual embolization of the hepatic artery and the portal venules supplying the tumor. Many important technical questions about TACE remain unanswered at this time: there are no reliable, standardized patient selection criteria, ideal cytotoxic agents have not yet been identified, the optimal dose of ethiodized oil has not been confirmed, and the optimal frequency and timing of repeat treatment sessions remain unknown. One major limitation of TACE—the need for repeated treatments, which can result in deterioration of liver function—may be avoided by use of a combination of interventional therapies. The combination of limited TACE with PEI or RFA may lead to improved survival and decreased risk of liver failure. More recently, two excellent randomized clinical trials have demonstrated significant survival benefit for patients treated with TACE when compared with those treated symptomatically.

## Acknowledgments

The authors thank Beth Wagner for assistance with extensive search of the literature, Stephanie P. Deming for editorial support, and Kelly R. Gurgos for assistance with preparation of the manuscript.

## References

[1] Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1999. CA Cancer J Clin 1999;49: 8–31.
[2] El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–50.
[3] Cancer of the Liver Italian Program investigators. A new prognostic system for hepatocellular carcinoma. a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998;28:751–5.
[4] Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999; 30:1434–40.
[5] Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325:675–80.
[6] Lai EC, Fan ST, Lo CM, et al. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. Ann Surg 1995;221:291–8.
[7] Nakakura EK, Choti MA. Management of hepatocellular carcinoma. Oncology (Huntingt) 2000;14:1085–98; discussion, 1098–102.
[8] Yamamoto J, Kosuge T, Takayama T, et al. Recurrence of hepatocellular carcinoma after surgery. Br J Surg 1996;83:1219–22.
[9] Jwo SC, Chiu JH, Chau GY, et al. Risk factors linked to tumor recurrence of human hepatocellular carcinoma after hepatic resection. Hepatology 1992;16:1367–71.
[10] Nagasue N, Uchida M, Makino Y, et al. Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. Gastroenterology 1993;105:488–94.
[11] Poon RT, Fan ST, Lo CM, et al. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg 1999;229:216–22.
[12] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
[13] Fong Y, Kemeny N, Lawrence TS. Cancer of the liver and biliary tree. In: Devita VTJ, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 6th edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 1162–1203.
[14] Lencioni R, Bartolozzi C, Caramella D, et al. Treatment of small hepatocellular carcinoma with percutaneous ethanol injection. Analysis of prognostic factors in 105 Western patients. Cancer 1995;76:1737–46.
[15] Livraghi T, Giorgio A, Marin G, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995; 197:101–8.
[16] Lencioni R, Pinto F, Armillotta N, et al. Long-term results of percutaneous ethanol injection therapy for hepatocellular carcinoma in cirrhosis: a European experience. Eur Radiol 1997;7:514–9.
[17] Lencioni R, Goletti O, Armillotta N, et al. Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. Eur Radiol 1998;8:1205–11.

[18] Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology 1999;210:655–61.
[19] Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954;30: 969–77.
[20] Bhattacharya S, Davidson B, Dhillon AP. Blood supply of early hepatocellular carcinoma. Semin Liver Dis 1995;15:390–401.
[21] Sparks FC, Mosher MB, Hallauer WC, et al. Hepatic artery ligation and postoperative chemotherapy for hepatic metastases: clinical and pathophysiological results. Cancer 1975;35:1074–82.
[22] Charnsangavej C, Chuang VP, Wallace S, et al. Angiographic classification of hepatic arterial collaterals. Radiology 1982;144:485–94.
[23] Doppman JL, Girton M, Kahn R. Proximal versus peripheral hepatic artery embolization experimental study in monkeys. Radiology 1978;128:577–88.
[24] Pelletier G, Roche A, Ink O, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990; 11:181–4.
[25] Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of ethiodized oil chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995;332:1256–61.
[26] Pelletier G, Ducreux M, Gay F, et al. Treatment of unresectable hepatocellular carcinoma with ethiodized oil chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol 1998;29:129–34.
[27] Matsuo N, Uchida H, Nishimine K, et al. Segmental transcatheter hepatic artery chemoembolization with iodized oil for hepatocellular carcinoma: antitumor effect and influence on normal tissue. J Vasc Interv Radiol 1993;4:543–9.
[28] Uchida H, Ohishi H, Matsuo N, et al. Transcatheter hepatic segmental arterial embolization using ethiodized oil mixed with an anticancer drug and gelfoam particles for hepatocellular carcinoma. Cardiovasc Intervent Radiol 1990;13:140–5.
[29] Matsui O, Kadoya M, Yoshikawa J, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. Radiology 1993;188:79–83.
[30] Andersson M, Aronsen KF, Balch C, et al. Pharmacokinetics of intra-arterial mitomycin C with or without degradable starch microspheres (DSM) in the treatment of non-resectable liver cancer. Acta Oncol 1989;28:219–22.
[31] Civalleri D, Esposito M, Fulco RA, et al. Liver and tumor uptake and plasma pharmacokinetic of arterial cisplatin administered with and without starch microspheres in patients with liver metastases. Cancer 1991;68:988–94.
[32] Soulen MC. Chemoembolization of hepatic malignancies. Oncology (Huntingt) 1994;8: 77–84; discussion, 84, 89–90 passim.
[33] Konno T. Targeting cancer chemotherapeutic agents by use of ethiodized oil contrast medium. Cancer 1990;66:1897–903.
[34] Egawa H, Mori K, Mitsuhashi S, et al. Effects of intraarterial chemotherapy using the new lipophilic anticancer agent "KM2210" (estradiol-chlorambucil) dissolved in ethiodized oil on Walker 256 carcinosarcoma in Wistar rats—a preliminary report. Eur Surg Res 1990;22:219–23.
[35] Nakamura H, Hashimoto T, Oi H, et al. Transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology 1989;170:783–6.
[36] Sasaki Y, Imaoka S, Kasugai H, et al. A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin, and gelatin sponge. Cancer 1987;60:1194–203.
[37] Daniels JR, Sternlicht M, Daniels AM. Collagen chemoembolization: pharmacokinetics and tissue tolerance of cis-diamminedichloroplatinum(II) in porcine liver and rabbit kidney. Cancer Res 1988;48:2446–50.
[38] Yumoto Y, Jinno K, Tokuyama K, et al. Hepatocellular carcinoma detected by iodized oil. Radiology 1985;154:19–24.

[39] Nakakuma K, Tashiro S, Hiraoka T, et al. Studies on anticancer treatment with an oily anticancer drug injected into the ligated feeding hepatic artery for liver cancer. Cancer 1983;52:2193–200.
[40] Goseki N, Nosaka T, Endo M, et al. Nourishment of hepatocellular carcinoma cells through the portal blood flow with and without transcatheter arterial embolization. Cancer 1995;76:736–42.
[41] Kan Z, Ivancev K, Hagerstrand I, et al. In vivo microscopy of the liver after injection of ethiodized oil into the hepatic artery and portal vein in the rat. Acta Radiol 1989; 30:419–25.
[42] Kan Z, Sato M, Ivancev K, et al. Distribution and effect of iodized poppyseed oil in the liver after hepatic artery embolization: experimental study in several animal species. Radiology 1993;186:861–6.
[43] de Baere T, Zhang X, Aubert B, et al. Quantification of tumor uptake of iodized oils and emulsions of iodized oils: experimental study. Radiology 1996;201:731–5.
[44] de Baere T, Dufaux J, Roche A, et al. Circulatory alterations induced by intra-arterial injection of iodized oil and emulsions of iodized oil and doxorubicin: experimental study. Radiology 1995;194:165–70.
[45] Kasugai H, Kojima J, Tatsuta M, et al. Treatment of hepatocellular carcinoma by transcatheter arterial embolization combined with intraarterial infusion of a mixture of cisplatin and ethiodized oil. Gastroenterology 1989;97:965–71.
[46] Majno PE, Adam R, Bismuth H, et al. Influence of preoperative transarterial ethiodized oil chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997;226:688–701.
[47] Takayasu K, Shima Y, Muramatsu Y, et al. Hepatocellular carcinoma: treatment with intraarterial iodized oil with and without chemotherapeutic agents. Radiology 1987;163: 345–51.
[48] Bartolozzi C, Crocetti L, Cioni D, et al. Assessment of therapeutic effect of liver tumor ablation procedures. Hepatogastroenterology 2001;48:352–8.
[49] Yamashita Y, Torashima M, Oguni T, et al. Liver parenchymal changes after transcatheter arterial embolization therapy for hepatoma: CT evaluation. Abdom Imaging 1993; 18:352–6.
[50] Ernst O, Sergent G, Mizrahi D, et al. Treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization: comparison of planned periodic chemoembolization and chemoembolization based on tumor response. AJR Am J Roentgenol 1999;172: 59–64.
[51] Leung DA, Goin JE, Sickles C, et al. Determinants of postembolization syndrome after hepatic chemoembolization. J Vasc Interv Radiol 2001;12:321–6.
[52] Chung JW, Park JH, Han JK, et al. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. Radiology 1996;198: 33–40.
[53] Gates J, Hartnell GG, Stuart KE, et al. Chemoembolization of hepatic neoplasms: safety, complications, and when to worry. Radiographics 1999;19:399–414.
[54] Bismuth H, Morino M, Sherlock D, et al. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. Am J Surg 1992;163:387–94.
[55] Jaeger HJ, Mehring UM, Castaneda F, et al. Sequential transarterial chemoembolization for unresectable advanced hepatocellular carcinoma. Cardiovasc Intervent Radiol 1996; 19:388–96.
[56] Liu CL, Fan ST. Nonresectional therapies for hepatocellular carcinoma. Am J Surg 1997; 173:358–65.
[57] Corr P, Chan M, Lau WY, et al. The role of hepatic arterial embolization in the management of ruptured hepatocellular carcinoma. Clin Radiol 1993;48:163–5.
[58] Liaw YF, Lin DY. Transcatheter hepatic arterial embolization in the treatment of hepatocellular carcinoma. Hepatogastroenterology 1990;37:484–8.

[59] Harnois DM, Steers J, Andrews JC, et al. Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for hepatocellular carcinoma. Liver Transpl Surg 1999;5:192–9.
[60] Colella G, De Carlis L, Rondinara GF, et al. Is hepatocellular carcinoma in cirrhosis an actual indication for liver transplantation? Transplant Proc 1997;29:492–4
[61] Schwartz ME, Sung M, Mor E, et al. A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg 1995;180:596–603.
[62] Wu CC, Ho YZ, Ho WL, et al. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. Br J Surg 1995;82:122–6.
[63] Izumi R, Shimizu K, Iyobe T, et al. Postoperative adjuvant hepatic arterial infusion of ethiodized oil containing anticancer drugs in patients with hepatocellular carcinoma. Hepatology 1994;20:295–301.
[64] Lai EC, Lo CM, Fan ST, et al. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. Arch Surg 1998; 133:183–8.
[65] Doppman JL, Girton M, Vermess M. The risk of hepatic artery embolization in the presence of obstructive jaundice. Radiology 1982;143:37–43.
[66] Pentecost MJ, Daniels JR, Teitelbaum GP, et al. Hepatic chemoembolization: safety with portal vein thrombosis. J Vasc Interv Radiol 1993;4:347–51.
[67] Charnsangavej C. Chemoemboization of liver tumors. Semin Invest Radiol 1993;10:150–60.
[68] Ikeda K, Kumada H, Saitoh S, et al. Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma. An analysis by the Cox proportional hazard model. Cancer 1991;68:2150–4.
[69] Takayasu K, Suzuki M, Uesaka K, et al. Hepatic artery embolization for inoperable hepatocellular carcinoma; prognosis and risk factors. Cancer Chemother Pharmacol 1989; 23(Suppl):S123–5.
[70] Hatanaka Y, Yamashita Y, Takahashi M, et al. Unresectable hepatocellular carcinoma: analysis of prognostic factors in transcatheter management. Radiology 1995;195:747–52.
[71] Vogl TJ, Trapp M, Schroeder H, et al. Transarterial chemoembolization for hepatocellular carcinoma: volumetric and morphologic CT criteria for assessment of prognosis and therapeutic success—results from a liver transplantation center. Radiology 2000; 214:349–57.
[72] Spreafico C, Marchiano A, Regalia E, et al. Chemoembolization of hepatocellular carcinoma in patients who undergo liver transplantation. Radiology 1994;192:687–90.
[73] Shimamura Y, Gunven P, Takenaka Y, et al. Combined peripheral and central chemoembolization of liver tumors. Experience with ethiodized oil-doxorubicin and gelatin sponge (L-TAE). Cancer 1988;61:238–42.
[74] Ngan H, Lai CL, Fan ST, et al. Treatment of inoperable hepatocellular carcinoma by transcatheter arterial chemoembolization using an emulsion of cisplatin in iodized oil and gelfoam. Clin Radiol 1993;47:315–20.
[75] Bronowicki JP, Vetter D, Dumas F, et al. Transcatheter oily chemoembolization for hepatocellular carcinoma. A 4-year study of 127 French patients. Cancer 1994;74: 16–24.
[76] Monden M, Okamura J, Sakon M, et al. Significance of transcatheter chemoembolization combined with surgical resection for hepatocellular carcinomas. Cancer Chemother Pharmacol 1989;23(Suppl):S90–5.
[77] Hashimoto T, Nakamura H, Hori S, et al. Hepatocellular carcinoma: efficacy of transcatheter oily chemoembolization in relation to macroscopic and microscopic patterns of tumor growth among 100 patients with partial hepatectomy. Cardiovasc Intervent Radiol 1995;18:82–6.
[78] Lin DY, Liaw YF, Lee TY, et al. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. Gastroenterology 1988; 94:453–6.

[79] Brown KT, Nevins AB, Getrajdman GI, et al. Particle embolization for hepatocellular carcinoma. J Vasc Interv Radiol 1998;9:822–8.
[80] Vetter D, Wenger JJ, Bergier JM, et al. Transcatheter oily chemoembolization in the management of advanced hepatocellular carcinoma in cirrhosis: results of a Western comparative study in 60 patients. Hepatology 1991;13:427–33.
[81] Simonetti RG, Liberati A, Angiolini C, et al. Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. Ann Oncol 1997;8: 117–136.
[82] Madden MV, Krige JE, Bailey S, et al. Randomised trial of targeted chemotherapy with ethiodized oil and 5-epidoxorubicin compared with symptomatic treatment for hepatoma. Gut 1993;34:1598–600.
[83] Yoshikawa M, Saisho H, Ebara M, et al. A randomized trial of intrahepatic arterial infusion of 4′- epidoxorubicin with ethiodized oil versus 4′-epidoxorubicin alone in the treatment of hepatocellular carcinoma. Cancer Chemother Pharmacol 1994;33(Suppl): S149–52.
[84] Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology 1998;27:1578–83.
[85] Trevisani F, De Notariis S, Rossi C, et al. Randomized control trials on chemoembolization for hepatocellular carcinoma: is there room for new studies? J Clin Gastroenterol 2001;32:383–9.
[86] Makuuchi M, Sukigara M, Mori T, et al. Bile duct necrosis: complication of transcatheter hepatic arterial embolization. Radiology 1985;156:331–4.
[87] Doppman JL, Dunnick NR, Girton M, et al. Bile duct cysts secondary to liver infarcts: report of a case and experimental production by small vessel hepatic artery occlusion. Radiology 1979;130:1–5.
[88] Chang JM, Tzeng WS, Pan HB, et al. Transcatheter arterial embolization with or without cisplatin treatment of hepatocellular carcinoma. A randomized controlled study. Cancer 1994;74:2449–53.
[89] Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35(5): 1164–71.
[90] Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734–9.
[91] Okuda K, Obata H, Nakajima Y, et al. Prognosis of primary hepatocellular carcinoma. Hepatology 1984;4(Suppl):3S–6S.
[92] Falkson G, Cnaan A, Schutt AJ, et al. Prognostic factors for survival in hepatocellular carcinoma. Cancer Res 1988;48:7314–8.
[93] Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999;29:62–7.
[94] Bartolozzi C, Lencioni R. Ethanol injection for the treatment of hepatic tumours. Eur Radiol 1996;6:682–96.
[95] Tanaka K, Nakamura S, Numata K, et al. Hepatocellular carcinoma: treatment with percutaneous ethanol injection and transcatheter arterial embolization. Radiology 1992; 185:457–60.
[96] Lencioni R, Vignali C, Caramella D, et al. Transcatheter arterial embolization followed by percutaneous ethanol injection in the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 1994;17:70–5.
[97] Koda M, Okamoto K, Miyoshi Y, et al. Combination therapy with transcatheter arterial embolization and percutaneous ethanol injection for advanced hepatocellular carcinoma. Hepatogastroenterology 1994;41:25–9.

[98] Bartolozzi C, Lencioni R, Caramella D, et al. Treatment of large HCC: transcatheter arterial chemoembolization combined with percutaneous ethanol injection versus repeated transcatheter arterial chemoembolization. Radiology 1995;197:812–8.
[99] Tateishi H, Kinuta M, Furukawa J, et al. Follow-up study of combination treatment (TAE and PEIT) for unresectable hepatocellular carcinoma. Cancer Chemother Pharmacol 1994;33(Suppl):S119–23.
[100] Lencioni R, Paolicchi A, Moretti M, et al. Combined transcatheter arterial chemoembolization and percutaneous ethanol injection for the treatment of large hepatocellular carcinoma: local therapeutic effect and long-term survival rate. Eur Radiol 1998;8:439–44.
[101] Koda M, Murawaki Y, Mitsuda A, et al. Combination therapy with transcatheter arterial chemoembolization and percutaneous ethanol injection compared with percutaneous ethanol injection alone for patients with small hepatocellular carcinoma: a randomized control study. Cancer 2001;92:1516–24.
[102] Goldberg SN, Hahn PF, Tanabe KK, et al. Percutaneous radiofrequency tissue ablation: does perfusion-mediated tissue cooling limit coagulation necrosis? J Vasc Interv Radiol 1998;9:101–11.
[103] Patterson EJ, Scudamore CH, Owen DA, et al. Radiofrequency ablation of porcine liver in vivo: effects of blood flow and treatment time on lesion size. Ann Surg 1998;227:559–65.
[104] Rossi S, Garbagnati F, Lencioni R, et al. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. Radiology 2000;217:119–26.